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COMMUNICATION

Improved Dissolution Rate of Indomethacin by Adsorbents

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ABSTRACT

Samples of indomethacin and kaolin or microcrystalline cellulose (Avicel) were prepared by solvent deposition or simple blending methods. Dissolution rates of these samples were studied. The surface adsorption of indomethacin on the studied adsorbents was shown to improve the dissolution rate of the drug in water. The solvent-deposited samples of indomethacin on kaolin or Avicel in the ratio 1:4 released 25% of the drug at 34 or 60 min, respectively ($t_{25\%}$), while 25% of the pure drug was released at 140 min. Meanwhile, the $t_{25\%}$ of the corresponding drug–adsorbent simple blends were 108 and 110 min, respectively. The effect of addition of polyvinyl pyrrolidone (PVP) as a third component to indomethacin–adsorbent was studied and showed further improvement in in vitro availability of the drug–kaolin adsorbents.

INTRODUCTION

The solubility characteristics of a drug are consistent with good adsorbability. For relatively insoluble drugs, the rate of dissolution is usually the rate-determining step in the overall absorption process. Reduction of particle size remains the accepted method for increasing dissolution rate (1). The antirheumatic agent indomethacin exhibits poor solubility. This undesirable physical property may increase the incidence of its irritating side effect on the gastrointestinal tract because of prolonged contact time with the mucosa. Numerous attempts (2–4) have been made to improve the dissolution rate of this widely used antirheumatic, in an effort to obtain more rapid and complete absorption. Surface adsorption is one of the methods used to reduce the drug particle size by increasing the surface area available to the dissolution medium. The technique of surface adsorption was first reported by Monkhouse and Lach (1). Recently, this technique has been employed to improve

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the dissolution characteristics of flufenamic acid using magnesium aluminum silicate and microcrystalline cellulose as adsorbents (5,6).

In our present study, attempts were made to modify the dissolution behavior and hence absorption of indomethacin by applying the surface adsorption with kaolin and microcrystalline cellulose (Avicel) as adsorbents. The effect of water-soluble polymer, polyvinylpyrrolidone (PVP), as a third substance was also investigated.

MATERIALS

Pure crystalline indomethacin (El-kahira Pharmaceutical and Chemical Co., Cairo, Egypt), kaolin (ICN Biomedicals, OH), microcrystalline cellulose (Avicel, pH 101, Sigma Chemical Co., St. Louis, MO) and PVP (MW 1000, GAF Corp., NJ,) were used in this study. All the materials were ground to a particle size < 125 μm, stored in a dessicator, and used for the entire study.

METHODS

Sample Preparation

By Solvent Deposition

Indomethacin was dissolved in a minimum volume of ethanol and the adsorbents (kaolin and Avicel) were then suspended in the alcohol solution. The calculated amount of PVP was added as a third component to some drug–adsorbent suspensions. The solvent was allowed to evaporate at room temperature until a dough mass was obtained. The residue was kept in a desiccator at room temperature. Samples were sieved and the fraction corresponding to particle size < 125 μm was used for the dissolution rate studies. By varying the quantity of the adsorbent and PVP, several samples were prepared.

By Simple Mixing

The drug and additive fractions of particle size < 125 μm were thoroughly mixed. Mixtures were sieved again and tumbled in a bottle for 10 min. Several samples were prepared corresponding to solvent-deposited samples.

Dissolution Studies

A six-channel dissolution apparatus II (Hanson Research Corp., Northridge, CA) with the paddle stirrer (USP XXII) was used. At zero time, 25 mg pure crystalline indomethacin or its equivalent of solvent-deposited powder or physical mixtures with the additives was sprinkled on the surface of 900 ml distilled water kept at 37°C and stirred at 50 rpm. At various time intervals, 5-ml filtered samples were withdrawn automatically and immediately replaced with fresh medium. Samples were assayed spectrophotometrically for indomethacin at 318 nm. At this wavelength, the additives did not interfere with the assay. The dissolution runs were duplicated.

RESULTS

The dissolution profiles of indomethacin from different adsorbate formulations are shown in Figs. 1 and 3 and Table 1. The results revealed that the dissolution rate of the drug was apparently increased by adsorbates. The drug in the absence of the adsorbent passed into solution very slowly. The release of indomethacin is known to be hindered by its hydrophobicity, resistance to wetting, and poor aqueous solubility.

Table 1 shows the dissolution parameters of indomethacin samples prepared by solvent deposition or simple blending. These parameters are 12% dissolution time ($t_{12\%}$), 25% dissolution time ($t_{25\%}$), 35% dissolution time ($t_{35\%}$), and the standard deviation (SD). They were determined from linear plots obtained by putting percentage dissolution on the logarithmic scale of a semilogarithmic paper (Figs. 2 and 4) according to Wagner dissolution model (7). These data are quite proper and provide convenient dissolution parameters for a given formulation to allow quantitative comparison with other formulations.

Figure 1 illustrates the dissolution rate profiles of indomethacin–kaolin adsorbates. It is clear that kaolin has improved the dissolution of the drug. The indomethacin–kaolin adsorbates (1:1 and 1:2) after 20 min showed 2.5-fold increase in the dissolution of indomethacin compared to the pure drug. Conversely, increasing the kaolin content in 1:3 and 1:4 adsorbates resulted in four-fold increase in drug dissolution after 20 min. It is not possible to attribute such increased dissolution rate entirely to the pH effects of the adsorbent in the microenvironment of the drug particles, since physical mixture samples of identical compositions showed only 1.25- and 1.7-fold increase, respectively, over the pure crystalline drug. The formation of an adsorbate is thus responsible in major part for such increased dissolution rates. In an adsorbate, the drug crystallizes on the

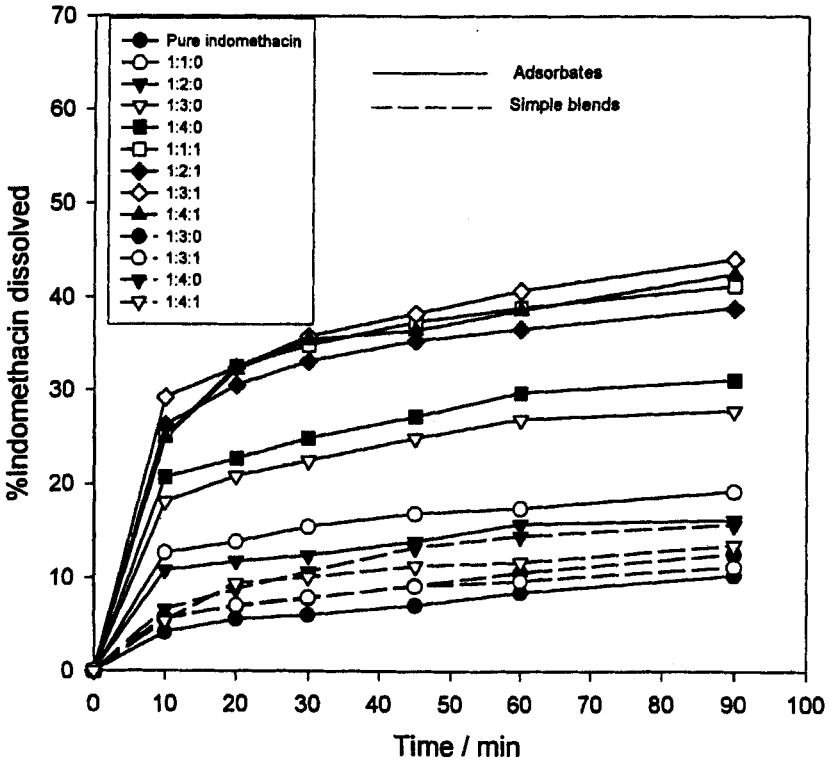

Figure 1. Dissolution profiles of pure indomethacin, indomethacin–kaolin:PVP adsorbates and indomethacin–kaolin:PVP simple blends, in water at 37°C.

Table 1

Dissolution Parameters for Indomethacin Samples as Obtained from the Semilogarithmic Plot

Composition	Kaolin				Avicel			
	$t_{12\%}$[a]	$t_{25\%}$	$t_{35\%}$	SD[b]	$t_{12\%}$	$t_{25\%}$	$t_{35\%}$	SD
Indomethacin:adsorbent:PVP								
1:1:0	6	100	140	0.0150	18	60	82	0.0180
1:2:0	24	130	170	0.0140	20	70	88	0.0185
1:3:0	–	54	100	0.0170	4	60	84	0.0174
1:4:0	–	34	84	0.0175	20	60	80	0.0183
1:1:1	–	–	40	0.0178	–	48	64	0.0192
1:3:1	–	–	34	0.0190	–	42	62	0.0177
Pure drug	84	140	160	0.0100	84	140	160	0.010
Simple blends								
1:3:0	70	140	168	0.0132	62	112	130	0.0145
1:3:1	80	176	190	0.0128	52	110	132	0.0147
1:4:0	46	108	136	0.0156	48	110	128	0.0153
1:4:1	44	118	148	0.0144	45	110	132	0.0159

[a]Time in minutes.
[b]Slope of the straight line.

surface of the adsorbent particles. Therefore, the ultimate achievement of fine particle production, i.e., its molecular size, gives appreciable increase in specific surface area and excellent dispersibility upon exposure to the dispersion medium (2). There is also the possibility of the formation of a drug solvate of higher dissolution during the preparation of the adsorbates (8). For indomethacin-kaolin adsorbates (1:3 and 1:4), the increased dissolution (four-fold after 20 min) in addition to the pH effect, is due to the greater surface area of kaolin available for the adsorption compared to the adsorbates of 1:1 and 1:2 compositions (9,10).

The samples 1:1, 1:2, 1:3, and 1:4 of indomethacin-kaolin adsorbates released 25% of their drug content after 100, 130, 54, and 34 min, respectively, compared to the pure drug ($t_{50\%}$ is 140 min) (Table 1 and Fig. 2).

The increase in the dissolution of indomethacin from the indomethacin-kaolin simple blends is because kaolin may have promoted deaggregation of the very fine indomethacin particle clumps in the dissolution medium resulting in a large effective drug-solvent interfacial area.

The dissolution profiles and data obtained for indomethacin-Avicel adsorbates are shown in Fig. 3 and Table 1. It is apparent that Avicel improved the dissolution of the drug. The indomethacin-Avicel adsorbates after 60 min showed three-fold increase in the dissolution of the indomethacin compared to the pure drug. Increasing the Avicel content in the samples from 1:1 to 1:4 did not alter greatly the dissolution behavior. This implies that the adsorbent surface was covered by a drug monolayer that controlled the dissolution process. On

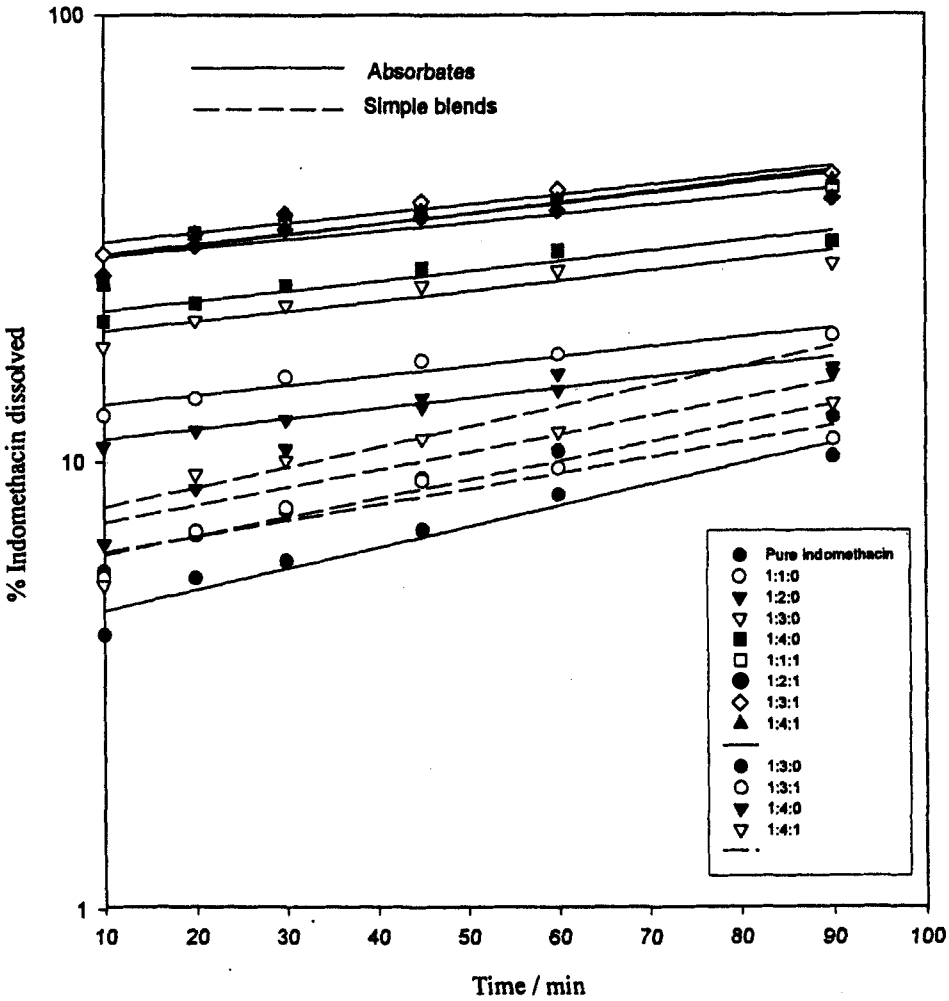

Figure 2. Semilogarithmic plot of dissolution rates of indomethacin:kaolin:PVP adsorbates and indomethacin:kaolin:PVP simple blends.

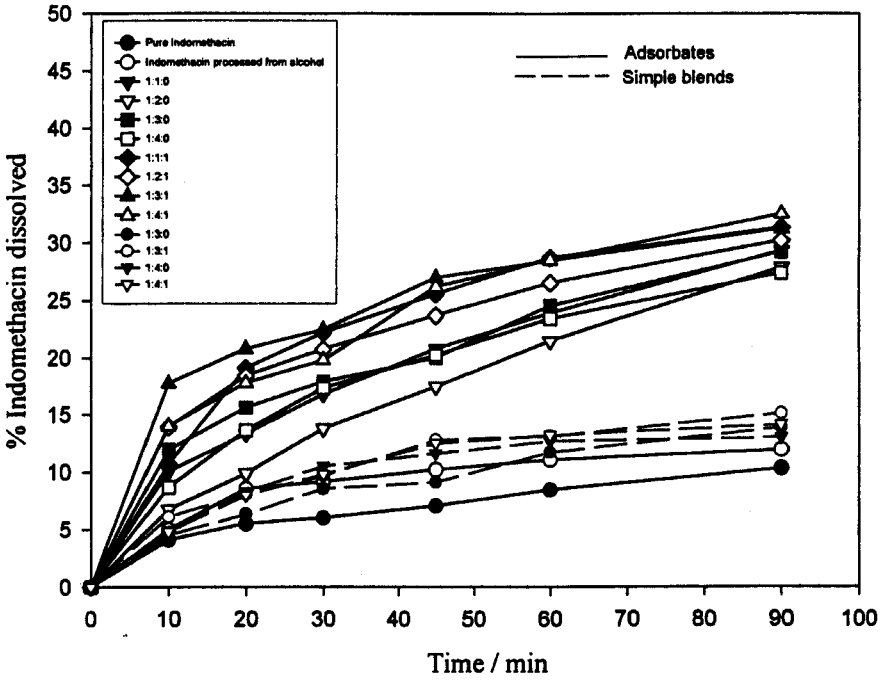

Figure 3. Dissolution profiles of pure indomethacin, indomethacin:Avicel:PVP adsorbates and indomethacin:Avicel:PVP simple blends, in water at 37°C.

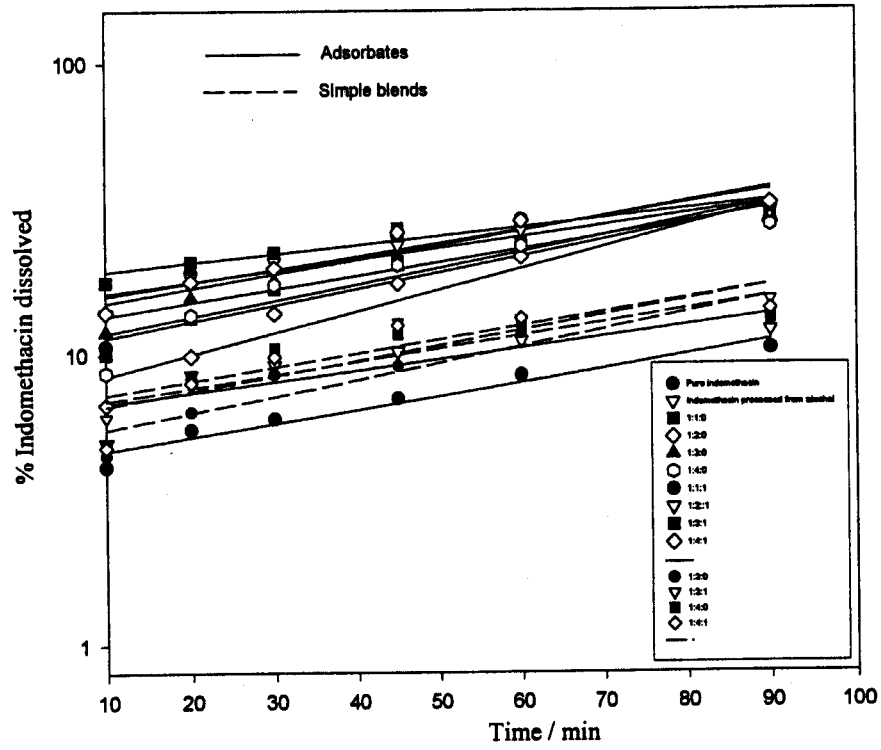

Figure 4. Semilogarithmic plot of dissolution rates of indomethacin:Avicel:PVP adsorbates and indomethacin:Avicel:PVP simple blends.

increasing Avicel concentration, multilayers coated the adsorbent surface or alternatively, the excess adsorbent coated the drug. Thus, when the samples were placed in the dissolution medium, the competition between the water molecules and the drug for Avicel surface became maximal once a monolayer was present. The dissolution rate was then minimally improved with further addition of adsorbent. Samples of 1:1, 1:2, 1:3 and 1:4 indomethacin–Avicel adsorbates released 25% of their drug content after about 60 min compared to the pure drug ($t_{50\%}$ is 140 min) (Fig. 4 and Table 1).

The increased drug dissolution rate from indomethacin–Avicel simple blends is due to the deaggregation of the indomethacin clumps achieved by Avicel in the dissolution medium (Fig. 3).

In the present formulation studies, aimed at optimizing drug release, it is usually required that complete drug release be achieved within a short period of time. It is apparent from Fig. 1 that the incorporation of PVP as a third component to indomethacin–kaolin deposited samples of different compositions (from 1:1 to 1:4) showed after 20 min a six-fold increase in the drug dissolution rate and released 35% of their drug content in about 34–40 min (Table 1). Meanwhile, the corresponding indomethacin–Avicel adsorbates showed after 20 min only a 3.5-fold increase and the time for releasing their 35% drug content was about 64–80 min (Table 1). The improvement of the dissolution rate on addition of PVP to the adsorbates may be attributed to its wetting and solubilizing effect. Takayama et al. (11,12) proved that water-soluble polymers, such as methylcellulose and PVP, gave adequate stabilization to the unstable supersaturation state showed by the dissolution profiles of indomethacin dispersed in crosslinked PVP. The stabilization of the supersaturation state of indomethacin will afford a high dissolution rate and an increase of bioavailability when samples are administered orally.

CONCLUSION

It has been shown that the surface adsorption of indomethacin to kaolin or Avicel can improve the dissolution rate of the drug in water. Moreover, simple blending of the drug with the studied adsorbents showed to a lesser extent an increase in the drug dissolution rate. Addition of PVP to indomethacin adsorbates resulted in a further improvement in the dissolution rate of the indomethacin–kaolin adsorbates.

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